REMARKS

I. Status Summary

Claims 1-45 are pending in the present application. Claims 1-45 currently stand rejected by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Claim 37 has been objected to by the Patent Office.

Claims 1-4, 6-8, 11, 15-19, 24, 26-29, 38-42, 44, and 45 have been amended. Claim 37 has been canceled. New claim 46 has been added. Support for the amendments and new claim can be found in the application as filed. No new matter has been added. Therefore, upon entry of Amendment C, claims 1-36 and 38-46 will be pending in the subject application.

Reconsideration of the application as amended and further in view of the remarks set forth hereinbelow is respectfully requested.

II. Claim Objections

Claim 37 has been objected to under 37 CFR 1.75(c), as being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim. In particular, the Patent Office contends that as a result of amendment to claim 1, the limitations of claim 37 seem to be found in claim 1 and that claim 37 does not further limit claim 1 from which it depends.

Applicants respectfully submit that claim 37 has been canceled herein. Accordingly, applicants respectfully believe that the Patent Office's objection has been addressed.

III. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-45 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Patent Office alleges that claims 1, 44, and 45 are indefinite with respect to what constitutes the metes and bounds of "approximately spherical." The Patent Office alleges that claim 1 is confusing as a result of redundant use of the clause "the target nucleic acid

sequence additionally comprises at least one nanoparticle attached to the target nucleic acid sequence." The Patent Office contends that claim 1 is indefinite with respect to the metes and bounds of "specifically hybridizes," "stringent hybridization conditions," "metal-atom entity," and "interband transition." The Patent Office alleges that the phrase "and exhibits one of surface plasmon resonance and an interband transition" is confusing and suggests that claim 1 be amended to recite "selected from the group consisting of."

The Patent Office contends that claims 1-45 are indefinite with respect to what constitutes the sequence of a "target nucleic acid sequence" as well as a "target sequence." The Patent Office contends that while a DNA or RNA may comprise a sequence of nucleotides, the polymer is but a single molecule. The Patent Office suggests using language to clarify that the target is a DNA, mRNA, polynucleotide, or nucleic acid and not a sequence.

The Patent Office contends that the term "derived" is confusing in claim 26. The Patent Office contends that claim 27 is indefinite with respect to "a sequence from a gene."

The Patent Office alleges that claim 28 is confusing because it states that the capture probe comprises or is suspected to comprise a mutation to be detected. The Patent Office suggests adopting language to show that the capture probe is directed against a target nucleic acid that comprises or is suspected to comprise a mutation.

The Patent Office alleges that claim 38 is confusing as the result of the use of the expression "one of." The Patent Office suggests using the phrase "selected from the group consisting of."

The Patent Office alleges that claim 45 is confusing for reciting "an at least least 10 fM concentration."

Finally, claims 1-45 have also been rejected under 35 U.S.C. § 112, second paragraph, for being incomplete for allegedly omitting essential steps. The Patent Office contends that the omitted step is performing a comparison temperature measurement step.

After careful consideration of the rejections and the Patent Office's comments, applicants respectfully traverse the rejections and offer the following remarks.

Initially, applicants respectfully submit that claim 37 has been canceled, thereby rendering the rejection with regard to claim 37 moot.

Applicants respectfully submit that the terms and phrases "approximately spherical," "specifically hybridizes," "stringent hybridization conditions," "metal-atom entity," "interband transition," target nucleic acid sequence," "target sequence," and "derived" would be clearly understood by one of skill in the art based upon the wording and subject matter of the claims, particularly after review of the instant specification. In particular, applicants respectfully submit that "specifically hybridizes" is described in the instant specification at page 37, lines 17-20. "Stringent hybridization conditions" are described in the instant specification at page 37, line 29 to page 39, line 16. For example, stringent hybridization conditions can refer to conditions wherein the probe hybridizes to its target sequence, but to no other sequence. See Instant Specification, page 38, lines 14-16. The application further recites that the terms "nucleic acid sequence," "nucleic acid" and "nucleic acid molecule" are being used interchangeably to refer to at least two nucleotides covalently linked together (i.e., an oligo- or polynucleotide). See Instant Specification, page 13, lines 15-17. The instant specification at page 10, lines 32-33 recites that a "target sequence" refers to a "nucleic acid sequence." However, in an effort to expedite allowance of the present application, applicants respectfully submit that these terms and phrases have been deleted from the presently pending claims.

More particularly, applicants respectfully submit that claims 1, 44, and 45 have been amended to delete "approximately." The phrase "is approximately spherical" has also been deleted from claim 11 to avoid redundancy with claim 1.

Claims 1 and 44 have been amended to delete the terms "specifically hybridizes" and "stringent hybridization conditions." Claims 1 and 44 have been amended to recite "the capture probe comprises an oligonucleotide that is complementary in whole or in part to the target nucleic acid." Support for the amendments can be found in the instant specification at page 20, lines 28-31, which

recites that oligonucleotide probes are generally designed to be complementary, in whole or in part, to a target sequence, such that hybridization between the target sequence and the probe or probes occur.

Claim 1 has been amended to delete the terms "metal-atom entity" and "interband transition." Regarding the nanoparticle, claim 1 has been amended to recite "comprises a material known to absorb light at one or more particular wavelength." Support for the amendment can be found in the instant specification as filed at page 11, line 29-31, which recites that the nanoparticle comprises a material that absorbs light at one or more particular frequencies; and at page 29, lines 14-15, which recites that a nanoparticle "can comprise any material, as long as the material is able to absorb light at a known wavelength."

Claims 1-4, 15, 16, 18, 19, 26, 29, 38, 39, 41, 42, 44, and 45 have been amended to replace the terms "target," "target sequence" or "target nucleic acid sequence" with the term "target nucleic acid," or to otherwise delete the term "sequence." Support for the amendments can be found in claims 1-4, 15, 16, 18, 19, 26, 29, 38, 39, 41, 42, 44, and 45 has filed. Additional support for these amendments can be found in the instant specification as filed at page 10, lines 32-33, which recites that a "target sequence" means a nucleic acid sequence, and at page 13, lines 15-17, which recites that the terms "nucleic acid" and "nucleic acid sequence" mean at least two nucleotides covalently linked together.

Claim 26 has been amended to recite a method wherein the target nucleic acid is selected from the group consisting of an mRNA and a cDNA. Support for the amendment can be found in claim 26 as originally filed.

Claim 27 has been amended to recite a method wherein the capture probe comprises an oligonucleotide from a gene of interest. Support for the amendment can be found in claim 27 as originally filed and in claim 1, which recites that the capture probe comprises an oligonucleotide.

Further, applicants respectfully submit that claims 1, 44 and 45 have been amended to delete the phrase "wherein the target nucleic acid sequence additionally comprises." Claims 1, 44, and 45 as amended each recite that the hybridization

complex comprises at least one nanoparticle component (c) that is attached to the target nucleic acid. Support for the amendments can be found in claims 1, 44 and 45 as filed.

Claim 28 has been amended to recite that the capture probe comprises a mutation to be detected. Applicants respectfully submit that support for the capture probe comprising a mutation can be found in the instant specification at page 56, lines 16-18, which recites that the mutation can be located on either the target sequence or on a probe sequence. With regard to the Patent Office's comments regarding claim 28, applicants respectfully note that, as described in the instant specification at page 55, line 6 to page 56, line 13, in methods related to gene expression, the target nucleic acid can be mRNA. When a mutation is present in the DNA that is transcribed to provide the target mRNA, the target mRNA can hybridize to a probe sequence that is designed based on the original DNA and to contain the same mutation. Accordingly, applicants respectfully submit that one of skill in the art, particularly after a review of the instant specification, would understand that a probe could be provided that comprises a mutation.

Claims 38 and 39 have both been amended to replace the phrase "one of" with the phrase "one of the group consisting of."

Claim 45 has been amended to delete one "least."

Finally, applicants respectfully submit that, although it is believed that the carrying out of a temperature comparison step can be inferred by claims 1, 44, and 45 as previously worded, claims 1, 44, and 45 have been amended herein to recite the steps of providing a background temperature of the solid surface in the absence of said complex and comparing the temperature of the solid surface detected in the presence of said complex with the background temperature, whereby detection of an increased temperature in the presence of said complex relative to the background temperature indicates the presence or amount of target nucleic acid in the sample, in an effort to expedite allowance of the claims. Support for the amendments can be found in claims 1, 44, and 45 as originally filed, which imply the providing of a background temperature of the solid surface in the absence of the hybridization

complex and the comparison of the background temperature with the temperature detected in the presence of the complex by reciting "detection of an increased temperature relative to a temperature of the solid surface that would be detected in the absence of said complex." Further support for the use of the term "background temperature" can be found in claim 2 as originally filed. Further support for the sample can be found in the instant specification at page 16, lines 23-29.

Thus, applicants respectfully submit that the Patent Office's comments regarding the definiteness and completeness of the claims have been addressed. Accordingly, applicants respectfully request that the rejections of claims 1-36 and 38-45 under 35 U.S.C. § 112, second paragraph, be withdrawn. Applicants respectfully ask that claims 1-36 and 38-45 be allowed at this time.

IV. Response to the Rejection under 35 U.S.C. § 101

Claims 1-45 have been rejected under 35 U.S.C. § 101 because the claimed subject matter is allegedly not supported by either a specific, substantial, or credible asserted utility or well established utility. In particular, the Patent Office alleges that, as presently worded, the claimed method can result in the detection of a nucleic acid such as an mRNA or corresponding cDNA, known as an expressed sequence tag or EST, for which no known utility exists. Further, the Patent Office alleges that, as presently worded, the claimed method has been construed as encompassing the detection of a target nucleic acid in a sample. The Patent Office contends that the sample may or may not actually comprise the target nucleic acid. The Patent Office alleges that since the method requires a "hybridization complex," the signal will always be positive, irrespective of the sample actually comprising the target sequence. The Patent Office suggests rewording the claim so that one can detect a target nucleic acid in a sample wherein the sample is suspected of comprising a target nucleic acid and the target nucleic acid is capable of forming the recited hybridization complex.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that, claims 1, 44, and 45 have each been amended to recite a method of detecting a target nucleic acid in a sample suspected of comprising the target nucleic acid, as suggested by the Patent Office. Claims 1, 44, and 45 have also been amended to recite "indicates the presence or amount of the target nucleic acid in the sample." Support for the target nucleic acid being in a sample can be found in the instant specification at page 16, lines 23-29. Further, as noted hereinabove, claim 37 has been canceled, thereby rendering the rejection of claim 37 moot.

Applicants respectfully submit that, generally, applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the requirement of 35 U.S.C. § 101. See *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977); and Manual of Patent Examining Procedure (hereinafter "MPEP") § 2107.02. Moreover, an assertion of utility is credible unless (a) the logic underlying the assertion is seriously flawed or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. See MPEP § 2107.02. Thus, the Patent Office bears the burden of making a *prima facie* showing that the claimed invention lacks utility, and to provide sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Id, citing *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664,666 (CCPA 1975).

Applicants respectfully submit that the Patent Office has failed to make a *prima facie* showing that one of ordinary skill in the art would not believe that the presently claimed methods of detecting a target nucleic acid have a specific, substantial or credible utility.

Applicants respectfully submit that the instant specification recites that the detection of nucleic acids, such as by the presently claimed methods, can be part of numerous techniques, including, for example, gene identification, mutation detection, gene expression profiling, and DNA sequencing. The instant specification also notes that diagnostic and forensic applications are but two areas in which nucleic acid

detection techniques find use. See Instant Specification, page 1, lines 22-26. The instant specification describes further how methods of detecting nucleic acids can be used in assays to diagnose chromosomal variations, cancer, and genetic abnormalities at page 54, lines 19-22. Array-related uses of the presently disclosed methods are described in the instant specification at page 54, lines 23-32. The instant specification describes in more detail how the presently disclosed methods can be used to monitor gene expression or to detect mutations at page 55, line 6 to page 56, line 18. Thus, applicants respectfully submit that one of skill in the art could readily appreciate the utility of the presently claimed methods.

With particular regard to the Patent Office's comments concerning the alleged lack of utility of detecting expressed sequence tags (ESTs), applicants respectfully submit that one of skill in the art would be aware of many uses of detecting ESTs. As described in Skrabanek et al. (*Nucleic Acids Research*, 29(21), e102 (2001); hereinafter "Skrabanek"; attached herewith as **Exhibit A**), ESTs have been used, among other things, to determine the expression profiles of genes. See Skrabankek, page e102, right-hand column, second sentence of first full paragraph. Thus, applicants respectfully submit that one of skill in the art would not have doubted the utility of the presently claimed methods because they might lead to the detection of an EST.

Finally, applicants respectfully submit that the capability of the target nucleic acid for forming the hybridization complex can be inferred by the wording of the claims. For example, claims 1 and 44 each recite that the target nucleic acid is hybridized to the capture probe and that the capture probe comprises an oligonucleotide that is complementary in whole or in part to the target nucleic acid. Claim 45 also recites that the capture probe comprises an oligonucleotide that is complementary to the target nucleic acid. As described in the instant specification as filed at page 20, lines 28-31, oligonucleotide probes are designed to be complementary, in whole or in part, to a target sequence, such that hybridization between the target and the probe occurs. As further described in the instant specification at page 20, line 32 to page 21, line 2, complementary sequences are

nucleotide sequences that are capable of pairing with one another upon the formation of hydrogen bonds between base pairs (i.e., hybridizing to one another). Applicants respectfully submit that one of skill in the art would understand, particularly after review of the instant specification, that the target nucleic acid and the probe oligonucleotide are capable of hybridizing to form the complex recited in claims 1, 44, and 45. Claims 2-36 and 38-43 each depend from claim 1, and, therefore, contain each and every element of claim 1. Thus, applicants respectfully submit that a target nucleic acid capable of forming a hydridization complex is also an element of claims 2-36 and 38-43.

Accordingly, applicants respectfully request that the present rejection of claims 1-36 and 38-45 under 35 U.S.C. § 101 be withdrawn and further ask that claims 1-36 and 38-45 be allowed at this time.

V. Response to Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-45 have been rejected under 35 U.S.C. § 112, first paragraph. The Patent Office contends that, since the claims are alleged not to be supported by either a specific, substantial and credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

After careful consideration of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Initially, as described hereinabove, applicants respectfully submit that claim 37 has been canceled, thereby rendering the rejection of claim 37 moot. As also described hereinabove, each of claims 1, 44, and 45 have been amended to recite a method of detecting a target nucleic acid in a sample suspected of comprising the target nucleic acid.

In view of the remarks submitted directly above with regard to the rejection under 35 U.S.C. § 101, applicants respectfully submit that the presently claimed methods of claims 1-36 and 38-45 are believed to be supported by a specific, substantial and credible utility. Accordingly, applicants respectfully request that the

rejection of claims 1-36 and 38-45 under 35 U.S.C. § 112, first paragraph, be withdrawn and further ask that claims 1-36 and 38-45 be allowed at this time.

VI. Other Amendments

In addition to the claim amendments previously described hereinabove, applicants respectfully submit that additional clarifying, non-limiting amendments have been made.

More particularly, claim 2 has been amended to recite "wherein the capture probe is attached to a solid surface at an attachment location," and to delete the final "to the solid surface." Support for "attachment location" can be found in claim 2 as filed. Claim 2 has also been amended to recite "attaching a detection probe to the first hybridization complex." Support for the "attaching" of a detection probe can be found in claim 41, which recites that the detection probe can be attached to the target nucleic acid after the target sequence hybridizes to the capture probe (i.e., forming the first hybridization complex of claim 2).

In view of the amendments to claim 1 to recite "a sample suspected of comprising the target nucleic acid," claim 6 has been amended to recite "wherein the sample is a biological sample." Support for the amendment can be found in claim 6 as filed.

Claim 7 has been amended to recite "the nanoparticle comprises one or more of the group consisting of a metal and a metal oxide." Support for the amendment can be found in claim 7 as filed.

Claim 8 has been amended to recite "a metal comprising one or more of the group consisting of gold, silver, and platinum." Support for the amendment can be found in claim 8 as filed.

Claims 2 and 16 have been amended to recite "the nanoparticle," in view of the recitation of a nanoparticle in claim 1.

Claim 17 has been amended to recite "the ligand-binding pair." Antecedent basis for the ligand-binding pair can be found in claim 16.

Claim 24 has been amended for grammatical purposes to delete the word "is."

Claims 38 and 39 have been amended to depend from claim 1 in view of the cancellation of claim 37.

Claim 40 has been amended to recite "the hybridization complex." Support for the amendment can be found in claim 1. Claim 40 has further been amended to recite "wherein the detection probe comprises the nanoparticle." Support for the detection probe comprising a nanoparticle can be found in the instant specification at page 11, line 15.

Claim 42 has been amended to recite "hybridizing the target nucleic acid to the capture probe to form a hybrid." Support for the amendment can be found in claim 42, which as originally filed recited "reacting the hybrid with a detection probe."

No new matter has been added. Applicants respectfully submit that claims 2, 6, 7, 8, 16, 17, 24, 38-40, and 42 are believed to be in condition for allowance and respectfully request a Notice of Allowance to that effect.

VII. New Claim

New claim 46 has been added. New claim 46 recites the method of claim 1, wherein the sample comprises a heterogeneous nucleic acid mixture and wherein providing the hybridization complex comprises providing hybridization conditions wherein the capture probe hybridizes to the target nucleic acid to the exclusion of other nucleic acids present in the sample.

Support for new claim 46 can be found in the instant specification at page 38, lines 14-16, which recites that under stringent hybridization conditions, a probe hybridizes to its target sequence, but to no other sequence. Further support can be found in the instant specification at page 37, lines 17-20, which recites that "specifically hybridizes" refers to hybridizing to only a particular nucleotide sequence when that sequence is present in a heterogeneous nucleic acid mixture.

No new matter has been added. Applicants respectfully submit that claim 46 is in condition for allowance and ask for a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

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